Reduced venous compliance in lower limbs of aging humans and its importance for capacitance function

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Olsen, Henrik, and Toste Länne. Reduced venous compliance in lower limbs of aging humans and its importance for capacitance function. Am. J. Physiol. 275 (Heart Circ. Physiol. 44): H878–H886, 1998.—Venous compliance in the calf of humans and its importance for capacitance function in relation to age were studied with the aid of 22, 44, and 59 mmHg lower body negative pressure (LBNP). Negative pressure transmission to the calf as well as changes in calf volume were studied, and venous compliance was calculated (change in volume with pressure change (dV/dP)). The change in capacitance response of the calf with age (20–70 yr) was evaluated during LBNP 44 mmHg. Transmission of negative pressure to the subcutaneous tissue was almost full without any changes with age (92%). However, it was reduced to 80% in the underlying muscle tissue, irrespective of depth. Venous compliance in the young was 0.051 ml·100 ml−1·mmHg−1 and was reduced by 45% to 0.029 ml·100 ml−1·mmHg−1 in the old (P < 0.05). Accordingly, the capacitance response was reduced by 0.015 ml·100 ml−1·yr−1 (P < 0.005). Furthermore, the hemodynamic response to hypovolemic circulatory stress was attenuated with age. The reduced pressure transmission in muscle tissue is probably due to restriction of the muscle fascia envelope. The reduced venous compliance with age and the concomitant reduction in capacitance response during LBNP have implications for both the sympathetic reflex responses as well as the capacitance response during acute hypovolemic circulatory stress, which might be defected in aging humans.

The venous section of the cardiovascular system can be looked upon as a voluminous blood reservoir designed to preserve a proper inflow of blood into the heart during various cardiovascular adjustments. The pronounced capacity of this reservoir implies that even small volume increases in the peripheral veins are followed by substantial differences in central blood volume.

Lower body negative pressure (LBNP) and tilting are experimental approaches used to pool blood in the capacitance vessels in the lower part of the body to create central hypovolemia in order to explore the baroreceptor as well as cardiopulmonary volume receptor function changes in aging. From these investigations a reduced efficiency has been proposed, which can result in more pronounced blood pressure alterations in the elderly, for example, in response to changes in body position (18). On the other hand, the sympathetic reflex responses to cold pressure tests have been shown to be unchanged. These apparent conflicting results might be due to an age-related reduction in the compliance of the cardiopulmonary walls, where volume (stretch) receptors are situated (10). However, an alternative explanation might be a decline of venous capacitance response with age in the lower limbs to LBNP, thereby reducing the decrease in central blood volume and thus the deactivation of baro/cardio pulmonary receptors. Ebert et al. (15) found less of a decrease in thoracic blood volume during similar levels of lower body suction in old compared with that in young individuals, suggesting less of a shift in thoracic blood volume to the lower extremities. This is in accordance with preliminary findings in our laboratory showing a reduction of 25% in the capacitance response of the legs between the ages of 20 and 60 yr during LBNP (22a).

The present study was conducted in order to validate the interpretation of the capacitance response in the calf during LBNP and its changes with age. First, the transmission of externally applied negative pressure to the underlying calf tissue as well as calf muscle viscoelasticity was evaluated in both young and old subjects, since differences in these aspects might change the interpretation of results. Second, venous compliance in the calf and the putative differences between young and old subjects were investigated. Finally, the capacitance response of the calf in response to LBNP was evaluated on a larger scale in healthy subjects of different ages.

MATERIALS AND METHODS

Experiments were performed on a total of 46 male volunteers (20–70 yr, median age 41 yr). Each subject gave informed consent to the experiments approved by the Ethics Committee of Lund University, Sweden. All subjects were healthy and average in being physically fit, without any previous history of cardiovascular diseases and without any medication. All were nonsmokers. The physical examination showed absence of hypertension, diabetes, or any other serious systemic diseases. Throughout the experiments, which lasted about 3 h, continuous efforts were made to maintain a relaxed, quiet atmosphere. Room temperature was maintained at 22–24°C. The experiments were started 1 h after a light meal in the morning or at noon.

Transmission of negative pressure to underlying calf tissue. In 11 subjects, 6 young (median age 22 yr, range 20–24 yr) and 5 old volunteers (median age 64 yr, range 60–66 yr), the transmission of external pressure to the underlying calf tissue was studied. With the volunteers placed in supine position, the skin and muscle fascia of the posterolateral muscle tissue compartment at the level of maximal circumference of the lower leg, ~15 cm distal to the knee, were anesthetized by 1–2 ml lidocaine (lignocain, 10 mg/ml, Astra, Södertälje, Sweden). A polyethylene catheter with an outer diameter of 1.7 mm was inserted perpendicular to the skin into the lateral gastrocnemius muscle (Venflon, Viggo Spectramed, Helsingborg, Sweden), and a 0.72-mm (internal diameter) Teflon catheter with four side holes (Myopress, Atos Medical, Hörby, Sweden) was inserted via the Venflon catheter after which the Venflon was withdrawn. The pressure
catheter was fixed with adhesive tape to the skin and connected to a pressure transducer (DT-XX disposable transducer, Viggo Spectramed), which was placed at the height that corresponded to the midpoint of the studied tissue segment of the calf ~5 cm below heart level. A three-way stopcock close to the pressure transducer was used to connect the pressure catheter to a pump (Perfuser Secura FT, B Braun, Kronberg, Germany) delivering saline 0.5 ml/h during the experiment to preserve catheter patency. In each subject, tests on the dynamic function of the pressure recording system were performed at the beginning of the experiment by applying external compression to the tissue and by asking the subject to perform active muscle contractions. These procedures normally resulted in rapid changes in the recorded pressure. When such tests occasionally produced unusually slow and small pressure deflections, or if there was a retrograde filling of blood into the catheter, it was taken as a sign of inadequate catheter patency. In these cases, the catheter was removed and a new one inserted at an adjacent site. The test with active muscle contractions was also performed at intervals between the experiments, and in a few cases there were signs of deterioration in catheter patency. Tissue pressure data from such recordings were omitted from the results presented below.

After insertion of the catheter at 4 cm depth, the legs were encased in an air-tight box up to the level of the iliac crest with a rubber seal fitted hermetically around the waist. The box was connected to a vacuum source (LBNP) permitting stable negative pressure to be produced. LBNP is a well-established technique in the study of orthostatic stress. The applied negative external pressure is transmitted into the tissue, causing an increase in transmural vascular pressure without more than transient effects on intravascular pressure (2, 27). Because compliance of the arterial bed is only ~3% of that of the venous bed, almost exclusively venous blood is pooled in the lower part of the body with the degree of pooling proportional to the negative pressure. The advantage of LBNP, compared with passive tilt, is that the subject remains at rest in the supine position, which facilitates physiological measurements and minimizes the likelihood of confounding activity in skeletal muscle. Furthermore, the transmural pressure change over the vascular walls is easier to detect than a change in venous pressure as the legs are raised, because similar shifts in blood volume, although the distribution of the pooled blood is probably not the same due to the differences in transmural pressure gradients (4, 37, 47). The subject was lying supine in the box with the left foot resting on a wooden plate to counter the forces created by the negative box pressure. Because muscle tension in the calf may affect muscle pressure and induce mechanical compression of the vascular tree, the right foot had no contact with the plate (43, 44). Care was taken to place the midpoint of the right calf 5 cm below heart level in all volunteers. To avoid any confounding external pressure, the lowest part of the calf was at least 2 cm above the floor of the vacuum chamber. After at least 60 min of supine rest, negative external pressure was rapidly instituted within 5 s and maintained for 3 min, thus allowing the ensuing tissue pressure change to stabilize at a steady level (see RESULTS). In between each period of reduced external pressure, tissue pressure was allowed to return to the control level. Repetitive analyses gave no indication that pressure transmission deteriorated with time or that control pressure increased with time due to possible edema formation. Tissue pressure was not affected by the discrete saline infusion, because no pressure changes were seen during arrested infusion. Pressure transmission was calculated from the measured tissue pressure change during LBNP, with the prevailing control level as baseline. At least two experiments were performed at each external negative pressure level of 30, 60, and 80 cmH2O corresponding to 22, 44, and 59 mmHg in each individual; i.e., levels within physiological limits, and the median values were calculated.

To evaluate the muscle viscoelasticity in the calf, the tissue pressure changes in response to a standardized linear change in external negative pressure of 4.2 mmHg/s from 0 to 42 mmHg (10 s) were measured. Then 10 s of stable 42 mmHg pressure followed, after which the applied negative external pressure was withdrawn from 42 to 0 mmHg in a standardized linear fashion with 4.2 mmHg/s (10 s). Combining these data made it possible to create a hysteresis function evaluating the viscoelasticity of the muscle tissue.

After the experiments at 4 cm depth, the catheter was withdrawn to a more superficial level of 2 cm depth but still within the muscle tissue. With the catheter in this position at least two 3-min experiments using rapidly instituted 44 mmHg were performed. Finally, a new pressure catheter was inserted with the same technique as described above but at a 30° angle to the skin into the subcutaneous adipose calf tissue at ~0.5 cm depth. The subcutaneous location of the catheter was easily controlled by palpation of the skin. Then a rapidly instituted 3-min LBNP 44 mmHg was performed.

To evaluate the muscle viscoelasticity in the calf, the tissue pressure as well as the pressure in the LBNP chamber was continuously measured by a manometer (DT-XX, Viggo Spectramed, Helsingborg, Sweden). The LBNP was changed or held constant by a rheostat.

Venous compliance of the calf. In 11 subjects [6 young (median age 22 yr, range 20–24 yr) and 5 old volunteers (median age 64 yr, range 60–66 yr)], the venous distensibility in response to changes in transmural pressure was studied. A mercury-in-Silastic strain gauge was applied at the maximal circumference of the calf ~15 cm distal to the knee. This method is designed for measuring volume changes of a limb by measurement of the circumference. A comparison with air-filled plethysmography has shown that reliable results may be obtained (6). A pressure catheter was inserted (as described above) 4 cm deep into the lateral calf muscle tissue within 3–4 cm from the applied strain gauge. The intramuscular pressure as well as the pressure in the LBNP chamber was measured as described above. At least 60 min of supine rest, rapidly instituted LBNP 22, 44, and 59 mmHg were produced (5 s) and held constant for 3 min, allowing the ensuing tissue pressure change to stabilize at a steady level, after which it was rapidly terminated. This evoked a rapid increase in leg volume (capacitance response). Because this is terminated within 3 min (42), it was defined as the calf volume increase from baseline to 3 min. Furthermore, the corresponding muscle pressure change at 3 min was calculated. In between each period of reduced external pressure, tissue pressure as well as calf volume was allowed to return to control level. At least two experiments at each level were performed in all individuals and the mean values were calculated. In each individual, the relationship between the increase in transmural pressure and capacitance response at LBNP 22, 44, and 59 mmHg could be characterized using linear regression. The individual curves in both young and old volunteers were then used to calculate the vascular compliance. Because the veins account for 97% of the vascular compliance, this is denoted venous compliance (Cv, ml·100 mmHg−1).

\[
C_v = \frac{\Delta V}{\Delta P}
\]  

where \(\Delta V\) denotes a change in calf volume (ml/100 ml) and \(\Delta P\) denotes a change in muscle pressure (mmHg).
Capacitance response to LBNP in relation to age. In 46 volunteers (median age 41 yr, range 20–70 yr), the capacitance response to changes in 44 mmHg of LBNP for 8 min was studied. Calf volume changes were measured as described above. The legs were enclosed in an air-tight box connected to a vacuum source permitting stable LBNP of 44 mmHg to be produced. Care was taken to place the midpoint of the right calf 5 cm below heart level in all volunteers. To avoid any confounding external pressure, the lowest part of the calf was at least 2 cm above the floor of the vacuum chamber. After at least 30 min of supine rest, negative external pressure was rapidly instituted within 5 s and maintained for 8 min. This evoked an initial rapid increase of leg volume (capacitance response) followed by a slower but continuous rise described from net transcapillary fluid transfer from blood to tissue. Because the capacitance response is terminated within 3 min, this was calculated from the volume increase at the onset of LBNP to the line defined from the capillary filtration slope between 3 and 8 min (42). At least two experiments were performed in each individual and the mean values calculated. In between each period of LBNP, tissue volume was allowed to return to the control level. Arterial blood pressure was measured noninvasively in the left upper arm with a semiautomatic blood pressure device (Omron, model HEM-700C, Tokyo, Japan). This device has been found to give accurate recording of the arterial blood pressure (14). Heart rate was measured with the aid of electrocardiogram, and this, as well as the pressure in the LBNP chamber, intramuscular pressure, and the changes in calf volume were amplified (Pc polygraph, Synetics Medical, Stockholm, Sweden) and collected with a modified computer program for medical examination (Gastrosoft polygram, Synetics Medical, Stockholm, Sweden) on a personal computer (SPC 386, SPC Trading, Uppsala, Sweden). Mean arterial blood pressure (MAP) was taken as the diastolic pressure plus one-third of the pulse pressure. The forearm blood flow was measured in the right forearm by standard venous occlusion (50 mmHg) strain gauge plethysmography (Hokanson EC-4, Hokanson, Washington). The data were given with reference to soft tissue resistance was calculated as MAP divided by blood flow pressure 1 min before measurements. A computerized R wave-triggered system was used for measurement of forearm blood flow using the three to six first heartbeats after the wave-triggered system was used for measurement of forearm blood flow (PRU). The data were given with reference to soft tissue weight excluding bone. Bone was taken as 10% of the studied calf volume (20).

Statistical analyses. Results are presented as median and interquartile range. The significance of difference between groups was tested with the aid of Mann-Whitney’s U-test. The relationship between age and capacitance response is presented with the aid of linear correlation.

### RESULTS

In the control state before experimental intervention, pressure in the posterior muscle compartment of the calf varied between 6.6 and 13.6 mmHg, median value 9.2, without any differences between the young and old groups. The muscle pressure was significantly higher (P < 0.05) than subcutaneous pressure (range 3.7–9.6 mmHg, median value 5.7). These baseline control observations at atmospheric pressure were in the same subject constant during the entire experiment, and the intersubject differences showed no correlation to the degree of transmission to the tissue of externally applied negative pressure.

Table 1 shows the background data on age, weight, and height and the hemodynamic response in percentage to the hypovolemic circulatory stress caused by LBNP 44 mmHg. This shows an attenuation in the old compared with the young volunteers.

Figure 1 shows the transmission in percentage of 59 mmHg externally applied negative pressure to the underlying muscle tissue in the posterior compartment of the calf at a tissue depth of 4 cm. It is evident from the depicted diagram that there was a rapid decline in tissue pressure at onset, and in the large majority of experiments a steady-state level had been reached already within 10 s and in all within 30 s. After reaching a steady state, it was seen that 80% of the externally applied negative pressure was transmitted to the underlying tissue both in the young (solid lines) and old individuals (broken lines). After cessation of negative external pressure, control tissue pressure was restored to 91% in the young and 64% in the old individuals within 10 s. The control tissue pressure was fully restored 30 and 60 s after cessation in the young and old, respectively. The tendency of a slower recovery to control tissue pressure in the old was also found at the other external pressure levels applied and was statistically significant (P < 0.05).

<table>
<thead>
<tr>
<th>Age Group</th>
<th>n</th>
<th>Age, yr</th>
<th>Body Weight, kg</th>
<th>Height, cm</th>
<th>HR, %</th>
<th>SBP, %</th>
<th>DBP, %</th>
<th>MAP, %</th>
<th>PP, %</th>
<th>FBF, %</th>
<th>PR, %</th>
</tr>
</thead>
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<td>21.6</td>
<td>70.0</td>
<td>181</td>
<td>141</td>
<td>94</td>
<td>103</td>
<td>99</td>
<td>81</td>
<td>42</td>
<td>240</td>
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<tr>
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<td>77.5</td>
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<td>123</td>
<td>100</td>
<td>103</td>
<td>101</td>
<td>96</td>
<td>59</td>
<td>174</td>
</tr>
<tr>
<td>Old</td>
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<td>64.0</td>
<td>81.0</td>
<td>180</td>
<td>118</td>
<td>98</td>
<td>102</td>
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Background data on age, weight, and height (presented on left) in subjects divided in 3 age groups, as well as hemodynamic responses to hypovolemic circulatory stress caused by lower body negative pressure of 44 mmHg (percentage of resting values, shown on right). LBNP, lower body negative pressure; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial blood pressure; PP, pulse pressure; FBF, forearm blood flow; PR, peripheral resistance. Significance calculations are based on comparisons between young and old groups. Values are expressed as median (25% percentile; 75% percentile).
There was no indication that pressure transmission deteriorated at high levels of negative external pressure and ~80% was transmitted in both groups also at 22 and 44 mmHg external negative pressure.

Figure 2 shows the transmission in percentage of 44 mmHg externally applied negative pressure to the underlying tissue at three different levels of tissue depths: 0.5 cm (subcutaneous adipose tissue), 2 cm (superficial muscle tissue), and 4 cm (deep muscle tissue). Because no differences between the young and old were seen in the pressure transmission at any depth, data from the two groups were compiled together. These data indicate differences in transmission between the subcutaneous and muscle tissue layers with an almost full transmission to the subcutaneous tissue (92%), whereas this was significantly lower (*P < 0.05) in the muscle tissue irrespective of depth (80%).

Figure 3 shows original recordings of muscle pressure changes in response to a linear increase (10 s) and a following decrease (10 s) in external negative pressure from 0 to 42 mmHg and 42 to 0 mmHg in one 24-yr-old (solid lines) and one 66-yr-old volunteer (broken lines). The hysteresis is a sign of muscle tissue viscoelasticity. No differences between the young and the old are seen during the increase in external negative pressure. However, during the decrease the muscle pressure changes are slower in the old compared with the young. This creates a larger hysteresis in the old and implies that the muscle tissue has stiffened with age. These differences between the young and old group of volunteers were statistically significant (*P < 0.05).

Figure 4A shows the venous compliance of the calf defined as increase in calf volume in response to changes in transmural pressure in the muscle tissue due to application of LBNP 22, 44, and 59 mmHg in the young (solid lines) and old individuals (broken lines), respectively. Comparison of the slope of the curves (ΔV/ΔP) in the young and old group of volunteers, i.e., the venous compliance, is shown in Fig. 4B. These data indicate a significant reduction of venous compliance with ~45% from 0.051 to 0.029 ml·100 ml⁻¹·mmHg⁻¹ in the old compared with the young (*P < 0.05). Resting muscle pressure in the individual subjects did not affect the compliance values.

Figure 5, left, shows a typical original tracing from a 21-yr-old volunteer illustrating tissue volume changes in the calf evoked by 44 mmHg LBNP. The initial rapid volume change reflects the capacitance response of 2.4 ml/100 ml. The subsequently much slower but continuous increase reflects net capillary filtration of plasma fluid into the tissue. A corresponding original tracing from a 60-yr-old volunteer is shown in Fig. 5.
right. Note the lower capacitance response of 1.7 ml/100 ml.

Figure 6 shows the cumulative data on the capacitance responses in the calf evoked by 44 mmHg LBNP in 46 volunteers at different ages (median age 41 yr, range 20–70 yr). Note the significant reduction with 0.015 ml·100 ml−1·yr−1 (P < 0.05).

**DISCUSSION**

This study shows that externally applied negative pressure to the calf is equally and almost fully transmitted to the subcutaneous tissue of the calf in both young and old healthy individuals. It is, however, somewhat reduced to 80% in the muscle compartment, probably due to restriction of the muscle fascia envelope. The venous compliance in the calf is reduced by 45% with age, with a concomitant reduction in capacitance response during LBNP.

Resting pressure levels in the muscle compartments of the leg have been shown to be ~5–9 mmHg in our study, as well as in others, with similar fluid-filled catheter systems used (2, 34, 44, 45). The differences between these data and the lower pressures found with wick catheters as well as implanted capsules seem to be related to the fact that the latter represents tissue fluid pressure, whereas the former represents total tissue pressure, e.g., a combination between fluid and solid pressures as defined by Guyton et al. (19). Another possibility for the fairly high muscle pressures found in this investigation could be due to the saline infusion in the catheter in order to preserve patency or due to a distortion in measurement by partial blockage of the catheter tip. This seems refuted, however, by the specific catheter system used as well as the precautions adopted (see **MATERIALS AND METHODS**). Also muscle pressure could have been increased due to fluid accumulation in the tissue after movements of the calf before the onset of experiments (26). The instructions given earlier to the participants made this unlikely, and at least 1 h of supine rest passed before the start of baseline registrations. Furthermore, baseline pressures were stable during the entire experiment.

We found an almost full transmission of the externally applied negative pressure to the subcutaneous tissue of the calf. However, it was slightly reduced in the underlying muscle tissue (80%) irrespective of depth (Figs. 1 and 2). This indicates that the muscle fascial envelope restricts the transmission somewhat in contrast to earlier findings in the upper arm of humans that did not show such a reduced transmission (28). In the upper arm this was true not only to ~40 mmHg, but to as much as ~100 mmHg, and independent of tissue depth down to 6.2 cm (28, 30). The difference between the two regions might be related to the fact that the calf, being a dependent region, needs a more firm fascial envelope in order to prevent edema formation due to capillary filtration in response to high transmural pressures. A more firm fascia may be one reason why compartment syndromes are sometimes seen in the lower leg but very seldom seen in the upper arm (32). Baseline muscle pressures were also higher in the calf (9 mmHg) compared with the upper arm (3 mmHg), although the same type of measuring equipment was used (28). Earlier studies on transmission of negative pressure to underlying tissue have shown somewhat divergent results. Coles (11) measured subcutaneous and intramuscular pressure changes in the calf, forearm, and hand at a tissue depth of 0.5–2.5 cm during external pressure reductions of ~50 to ~250 mmHg. Slightly <90% was transmitted in the calf at ~50 mmHg; however, subcutaneous and intramuscular pressure measurements were lumped together, which might be the reason why the transmission of pressure was somewhat higher in Coles’ than in ours (80%, Fig. 1). This is corroborated by the fact that his measurements on the hand (subcutaneous) at ~50 mmHg showed a transmission exceeding 95%. Ludbrook et al. (25) analyzed the transmission of negative pressure applied to the neck in humans and found only 64% transmission to the underlying tissue, independent of depth. Clausen et al. (9) also found a reduced transmission (46%) to the
renal parenchyma immediately below the renal capsule. In both studies the applied external pressure level was similar to ours. Thus it is obvious that tissue support varies between different anatomical areas. With higher levels of negative pressure, the transmission shows some deterioration (11), although this was not seen in our study up to −59 mmHg. Because total tissue compliance must have limitations, probably determined mainly by fascial envelopes, it is not surprising that pressure transmission may be impaired, especially at higher levels of external negative pressure. Transmission of negative pressure to the underlying muscle tissue could be altered with age due to an increase in collagen content of the muscle tissue with a decrease in elasticity (1). This seems refuted by the fact that ~80% of the negative pressure was transmitted in both the young and the old (Fig. 1). An interesting observation, however, was that there was a time lag with a slower recovery to baseline pressure after termination of the applied negative pressure in the old individuals (Fig. 1). The reason might be a reduced viscoelasticity of the muscle tissue as seen in the larger hysteresis during pressure change in the old individuals (Fig. 3). This reduced viscoelasticity could be due to an increase in collagen content in the muscle, as well as a change in the relationship between type I and type II muscle fiber that occurs with age (23).

The venous section of the cardiovascular system can be looked upon as a voluminous blood reservoir designed to preserve a proper inflow of blood into the heart during various cardiovascular adjustments. This section contains 85% of the total blood volume based on data from nonhuman species, and 70% of this is in the systemic veins and 15% in the heart and lungs (38). The pronounced capacity and low resistance of this reservoir imply that even small pressure reductions in the central veins are followed by substantial mobilization of blood from peripheral vascular beds toward the heart. Thus the central venous pressure and the filling of the heart may be maintained at a fairly stable level, despite variations in venous blood volume. Although in vivo experiments on human hand veins have provided evidence for sympathetic constrictor responses, both via α1-adrenoreceptor agonists and neuropeptide Y (24), no evidence exists that active venoconstriction of capacitance vessels in skeletal muscle (40–45% of the body weight) provides an important mechanism translocating blood to the central circulation (18). Thus the main part of the venous reservoir is adjusted simply by means of passive changes.

The stiffness of a vein can be ascribed quantitatively in terms of a relationship between its volume and distending (transmural) pressure. Compliance is described as the slope of the volume-pressure relationship \( \frac{\Delta V}{\Delta P} \). This is nonlinear and that is why compliance is variable and depends on distending pressure. At low pressures, the curve is steep, meaning that a large change in volume accompanies only a small change in pressure so that compliance is high. At higher pressures the slope is less steep and compliance is lower (46). The early phase of expansion of the veins involves no actual stretch of the elastic material in their walls, and a small change in distending pressure merely changes
the geometry of the veins (31, 35). Once the veins have assumed a circular cross section, subsequent increases in their transmural pressure are opposed by the development of increased tension in the walls. Because no measurement of the baseline venous pressure was performed, this might be a confounding factor in the study of venous compliance, although care was taken to place the calves at the same level, i.e., 5 cm below the heart. However, the part of the compliance curves that was studied from the calves (within the transmural pressure increase of 18–51 mmHg) was fairly linear (Fig. 4). This indicates that the venous section containing the majority of the blood volume, i.e., the venules, has assumed a circular cross-sectional area. Thus a comparison of compliance curves within this transmural pressure interval seems to be justified.

The volume-pressure curve of a limb at rest represents the distributed properties of all veins (microvessels to large veins). Other factors besides venous properties may affect this curve, such as rigid fascia that restricts expansion, especially in the upper part of the curve. However, this does not seem to be the case in the investigated pressure range, since no deterioration in pressure transmission was found with increasing pressure (−59 mmHg, Fig. 1). In the lower part of the volume-pressure curve, extensive tethering of veins may limit their emptying. The volume-pressure relationship will also be affected by the vascular anatomy, which determines how large a fraction of the total volume that is distributed within the smallest veins as opposed to the largest ones. A complex and undefined distribution of compliances exists between the smallest venules and the largest veins. This means that total venous compliance of the limbs depends on the size, relative number, and the wall structure of each venous segment. Another factor of importance is the resting state of the muscles, since muscle contraction increases muscle pressure and affects the venous compliance. Furthermore, the pressure increase is more pronounced at increasing depth, which indicates that the distribution of compliances within the muscles might change (13, 44).

Humans spend a large fraction of their lives in upright posture, and the problem of hydrostatic pooling would be eliminated if veins were as stiff as arteries. However, this would also eliminate the capacitance function of veins that allows substantial loss of blood with only small changes in venous as well as arterial pressure. In fact, this crucial first line of defense comes into play within seconds during an acute hypovolemic circulatory stress (29). The shape of the venous volume-pressure curve represents a compromise in design to meet two requirements. The compliant portion of the venous volume-pressure curve, which is the principal culprit in human orthostatic intolerance, is also the feature that permits our adjustment to blood loss. At higher pressures besides those investigated in our study (Fig. 4), further pooling in the legs is restricted, since the slope of the curve flattens at −40–60 mmHg, probably due to recruitment of collagen fibers in the venous walls (12), although restriction of the fascia envelope might also play a role. Without the stiffer portion of the volume-pressure curve, upright posture without hypotension would be impossible (39).

Venous characteristics vary markedly from region to region in such a way that the hydrostatic forces associated with upright posture are partially counteracted (37). In dependent regions of humans there is a thickening of the vein walls that tends to oppose some of the hydrostatic pressure encountered during upright posture. In contrast, veins near or above heart level are thin-walled and more distensible (39). Thus Schaper et al. (41) found a higher venous compliance in the forearm compared with that found in our investigation of the calf. The distribution of blood volume in various parts of the body is determined by the size of the veins and their vascular compliance, and also by the fraction of cardiac output they receive.

When the capacitance response to an increase in transmural pressure is studied, it is of fundamental importance to be able to separate the filling of the capacitance vessels from the capillary filtration. This is aided by the fact that the capacitance response is a rapid process, whereas the capillary filtration is fairly slow (Fig. 5). Furthermore, the capacitance response is terminated within ~3 min (42). Thus the differentiation between the two processes was defined in our study by the filtration slope between 3 and 8 min (Fig. 5).

The pronounced capacity of the venous system implies that even small transmural pressure changes in the peripheral veins lead to volume changes and, thus, are followed by substantial differences in central blood volume. LBNP and tilting are experimental approaches used to pool blood in the capacitance vessels in the lower part of the body to create central hypovolemia in order to explore baroreceptor as well as cardiopulmonary volume receptor function changes in aging. These have shown signs of reduced efficiency, which can result in more pronounced blood pressure alterations in the elderly, for example, in response to changes in body position (16). On the other hand, the sympathetic reflex responses to cold pressure tests have been shown to be unchanged (10). An explanation of these apparent conflicting results might be a reduced compliance of the cardiopulmonary walls, where volume (stretch) receptors are situated, since an attenuated reduction in left ventricular diastolic diameter is seen in the heart with age during hypovolemic stress caused by LBNP (10). However, an alternative explanation might be a decline of venous capacitance response with age in the lower limbs to LBNP, thereby reducing the decrease in central blood volume and thus the deactivation of baro-/cardiopulmonary receptors. Ebert et al. (15) found less of a decrease in thoracic blood volume during similar levels of lower body suction in old compared with young individuals, suggesting less of a shift in thoracic blood volume to the lower extremities. This is in accordance with the presented data in this study as well as earlier findings in our laboratory showing a reduction in venous compliance with a concomitant decrease in capacitance response with age (Figs. 4–6) (22a). Fur-
thermore, an age-related decrease in venous distensibility in the arms has also been shown by Gasco et al. (17).

The capacitance response of the lower limbs in response to LBNP decreased with age (Figs. 5 and 6). This could be a result of several factors. The differences in body weight between the groups, with a larger weight in the old, might introduce an error in the estimation of soft tissue-to-bone ratio (Table 1). An increased amount of soft tissue in the calf would indicate an overestimation of the capacitance response and an underestimation of the differences between the groups. Furthermore, a muscle atrophy may occur with aging, although no change in resting calf muscle pressure was seen (see RESULTS). This seems to increase compliance and would thus also lead to an underestimation of the differences in capacitance response between young and old (7). Another confounding factor might be differences in venous filling before LBNP. The capacitance of an anatomical area relates the total volume contained within the vasculature to the prevailing transmural pressure. However, in our experiments no measurements were made of the blood amount held in the calf before the application of suction ($V_0$), and there is no reason to believe that this volume is constant. To avoid inappropriate differences in $V_0$ between individuals, care was taken to place the calves at the same level. Furthermore, the volunteers rested at least 30 min before institution of external negative pressure during which time calf volume as well as blood flow to the limbs became stabilized (see MATERIALS AND METHODS).

Our experiments were then concerned with the extra volume contained within the vasculature to the prevailing pressure gradient of $\sim 10–15$ mmHg between the postcapillary vessels and the heart. Because of their high compliance, small changes in intravascular pressure, owing to changes in blood flow, will have marked effects on venous volume. During LBNP, arteriolar resistance increases by sympathetic stimulation of the arterial smooth muscle and the flow tends to decrease (47). This in turn decreases the pressure gradient from capillaries to large veins and the average small vein pressure decreases (38). This train of events probably occurs during LBNP, even if no change in large venous pressure is detected (2). Because the decrease in blood flow is attenuated in the elderly (Table 1), this might lead to differences between the groups with a relative increase in venous volume in the old (38). This, however, would result in an underestimation of the differences in capacitance response. Thus the conclusion is reached that decline in venous capacitance with age is valid and may be responsible for an attenuation of the hemodynamic response with a less marked increase in heart rate and peripheral resistance and an attenuated decrease in systolic blood pressure, pulse pressure, as well as forearm blood flow as seen in the old during LBNP (Table 1). Frey and Hoffler (16a) did not find any significant reduction of the capacitance response in the lower limbs with age. However, the age range in their study was much less than in ours, making the putative differences more difficult to detect. A possible explanation for the capacitance decline might be the increase in collagen-to-elastin ratio as well as wall thickening found in the veins with age (5) with a stiffening as a consequence analogous to the known increase in arterial wall stiffness with age (21). In addition, the differences in venous compliance and capacitance may be further increased by a lower fitness in old compared with young individuals (33, 36). The pathophysiological significance of the changes in the venous system with age is not known at present, but presumably it affects the blood volume homeostasis in such a manner that the decreased venous compliance centralizes the blood volume. This line of events has been suggested to be one factor in the development of essential hypertension (22, 40). Furthermore, the reduced compliance implies that the capacitance response during acute hypovolemic circulatory stress might be defective. Being the first line of defense in the preservation of homeostasis (29), this might seriously impede the possibility to survive acute blood loss in an aging individual.

In summary, externally applied negative pressure to the calf was equally transmitted in both the young and old and almost fully to the subcutaneous tissue. It was, however, somewhat reduced to 80% in the muscle tissue probably due to restriction of the muscle fascia envelope. The venous compliance was reduced by 45% in the lower limbs with age with a concomitant reduction in capacitance response during LBNP. Thus the central hypovolemic stimulus decreases, which might at least in part explain the declining reflex responses with age in humans. Furthermore, the reduced compliance implies that the capacitance response during acute hypovolemic circulatory stress may be defective, which might seriously impede the possibility to survive acute blood loss in an aging individual.

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REFERENCES
